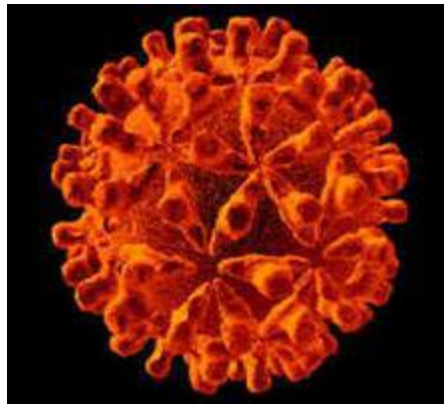

Hepatitis C Choices in Care

Overview Of Hepatitis C Virus Infection And Its Effects On The Body

Douglas LaBrecque, MD, FACP



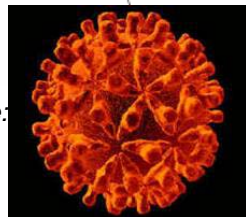
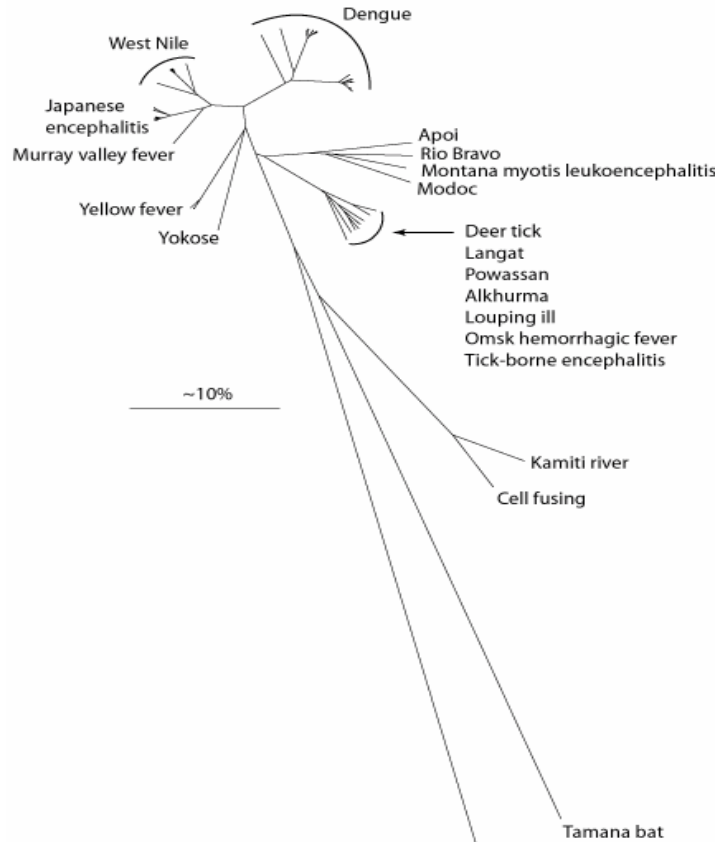
THE VIRUS



Hepatitis C Virus

- What is it?
- What does it look like?
- What is it made of?
- How does it get into liver cells and reproduce?
- Why is it so hard to get rid of?

HCV is a Flavivirus



Properties

Single strand RNA

Enveloped

Spheroidal: 40-60 nm in diameter.

Surface projections (appears rough)

3 structural proteins

Variable number of non-structural proteins



Carl Linnaeus 1739

Courtesy of HCV sequence database:

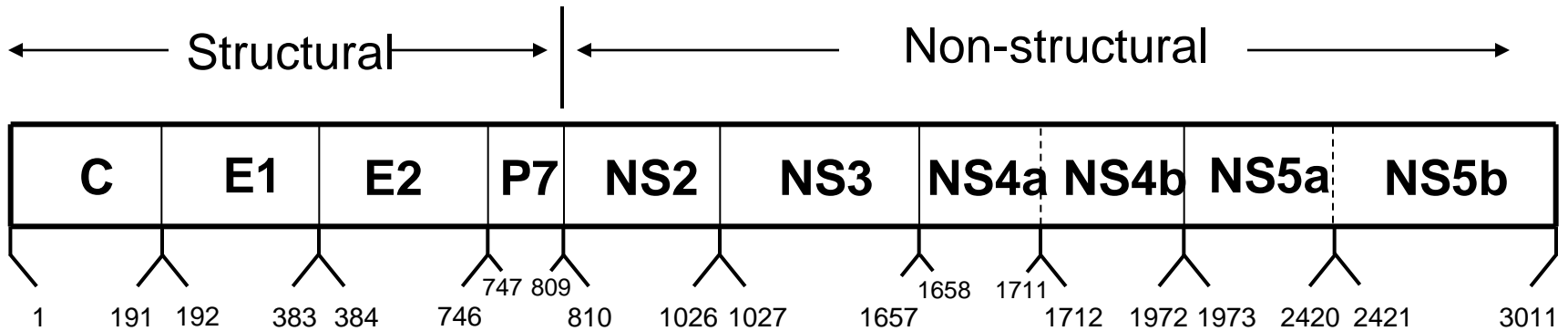
<http://hcv.lanl.gov>

And The Linnaean Society of London

HCV (a distant family member – (a hepacivirus))

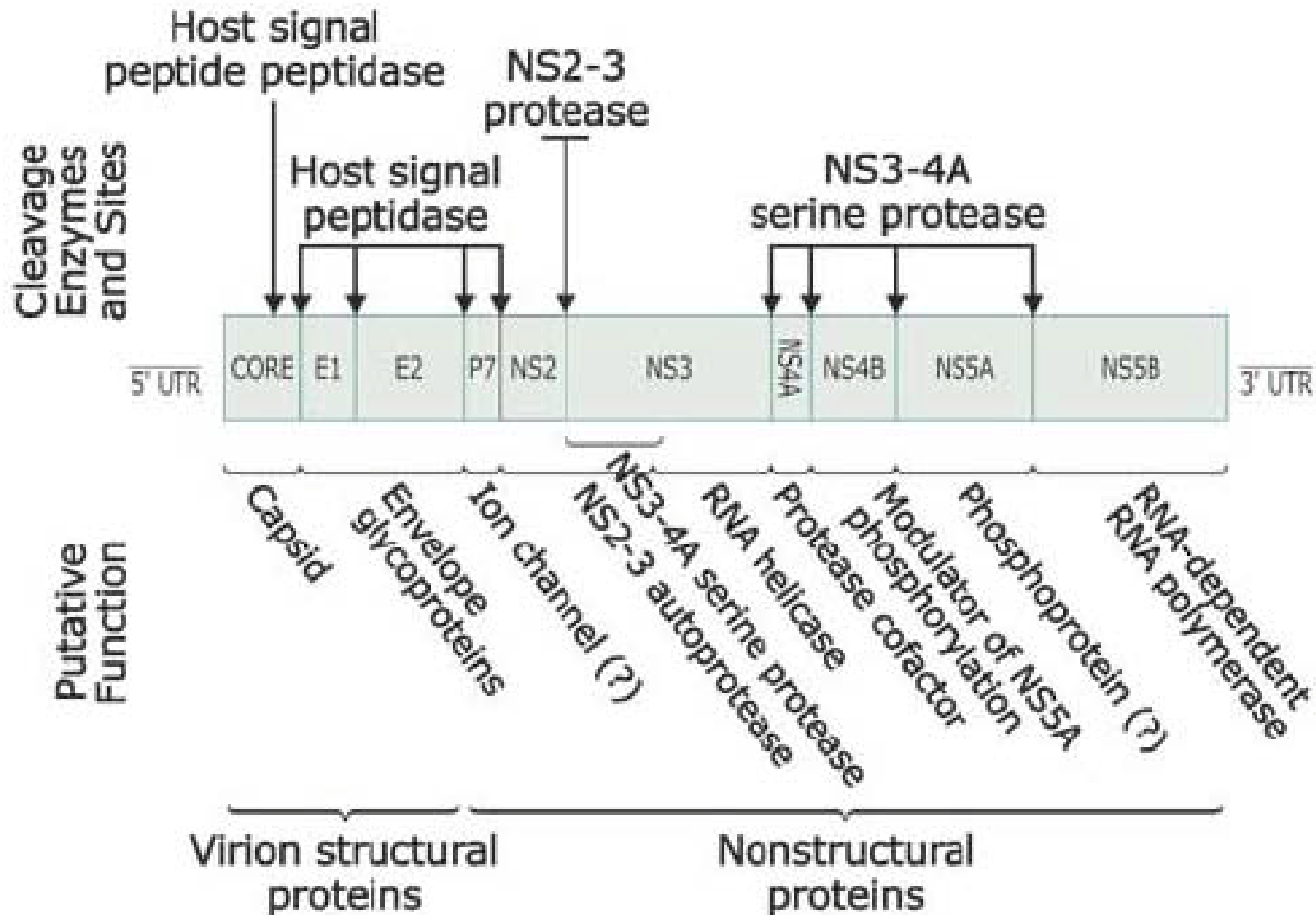
Choo et al. Science 1989: 244.359-62

HCV-1 Protein Structure



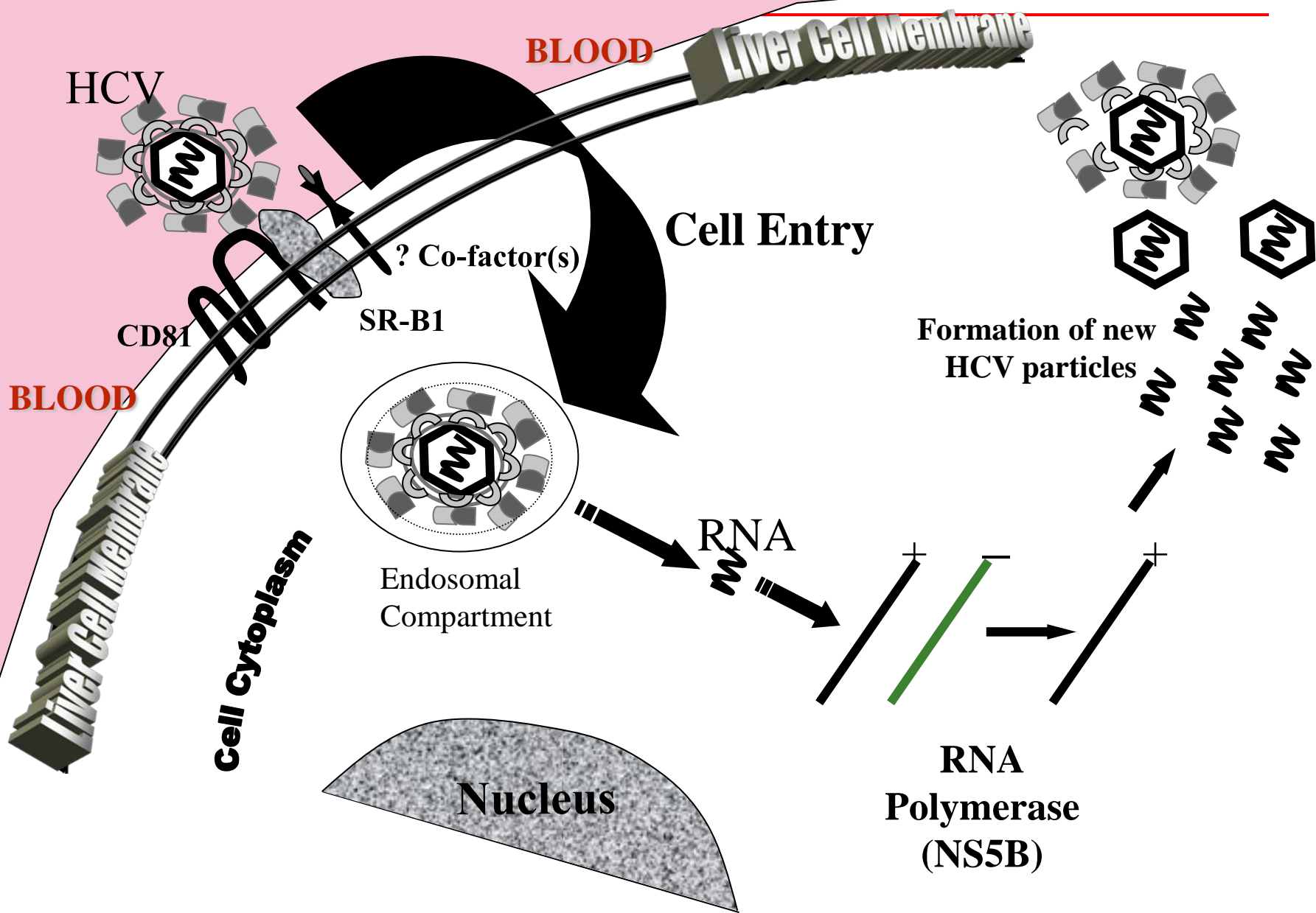
- **9.6 kb + RNA Open Reading Frame**
- **3010-3033 Amino Acid Polyprotein Precursor (HCV-1= 3011)**
- **10 Proteins: Structural and Nonstructural**

Known Functions of the HCV Proteins



HCV Life Cycle

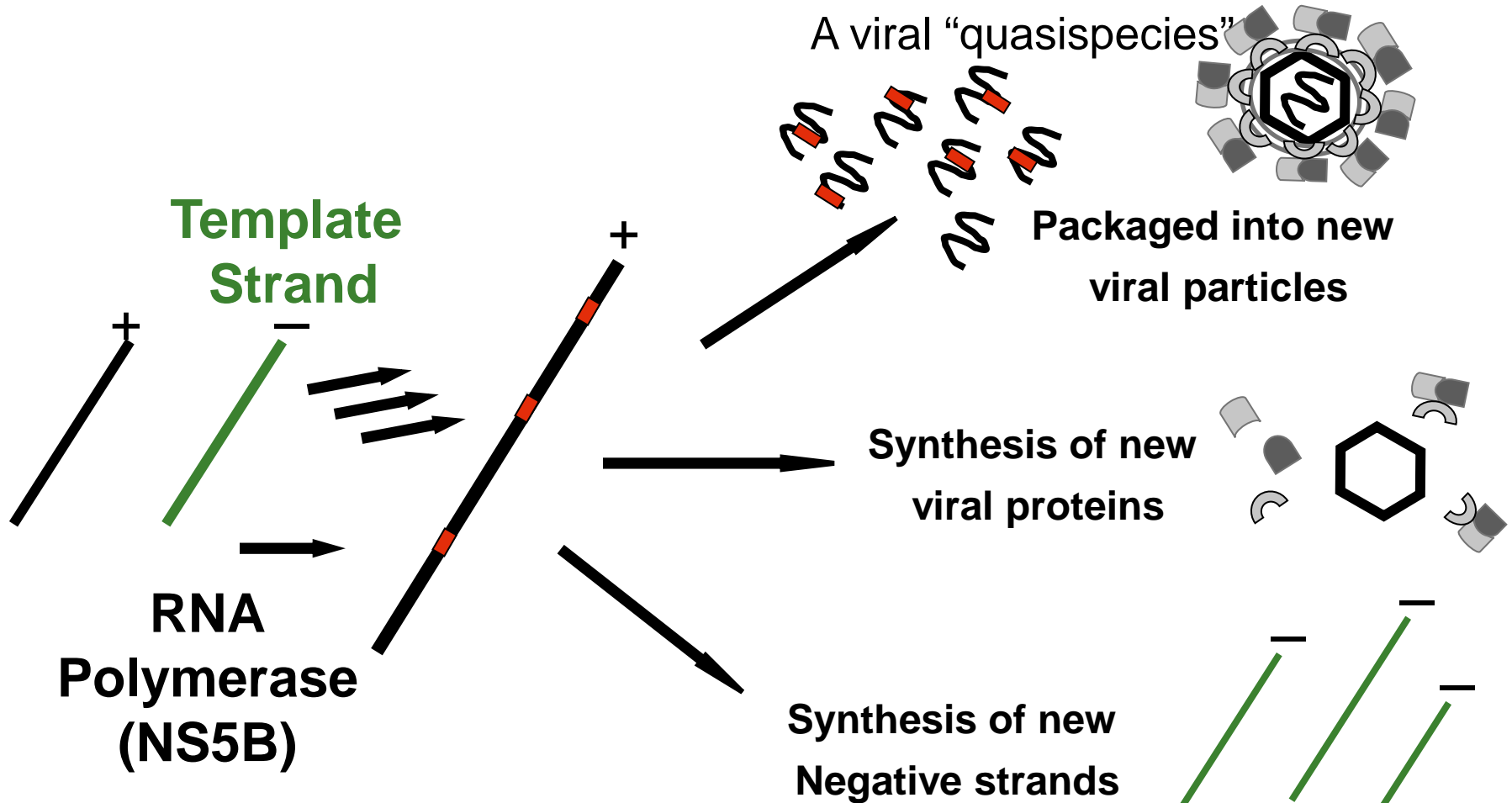
- HCV entry into a liver cell
- The single strand of + sense viral RNA is released:
- + RNA strand makes a mirror image of itself: a – (negative) strand
- – RNA strand provides a template on which many + strands are synthesized:
 - Three potential avenues for a new + strand:
 - Viral protein synthesis (following attachment to host ribosomes)
 - Packaged to form new HCV particles
 - Formation of further negative strands



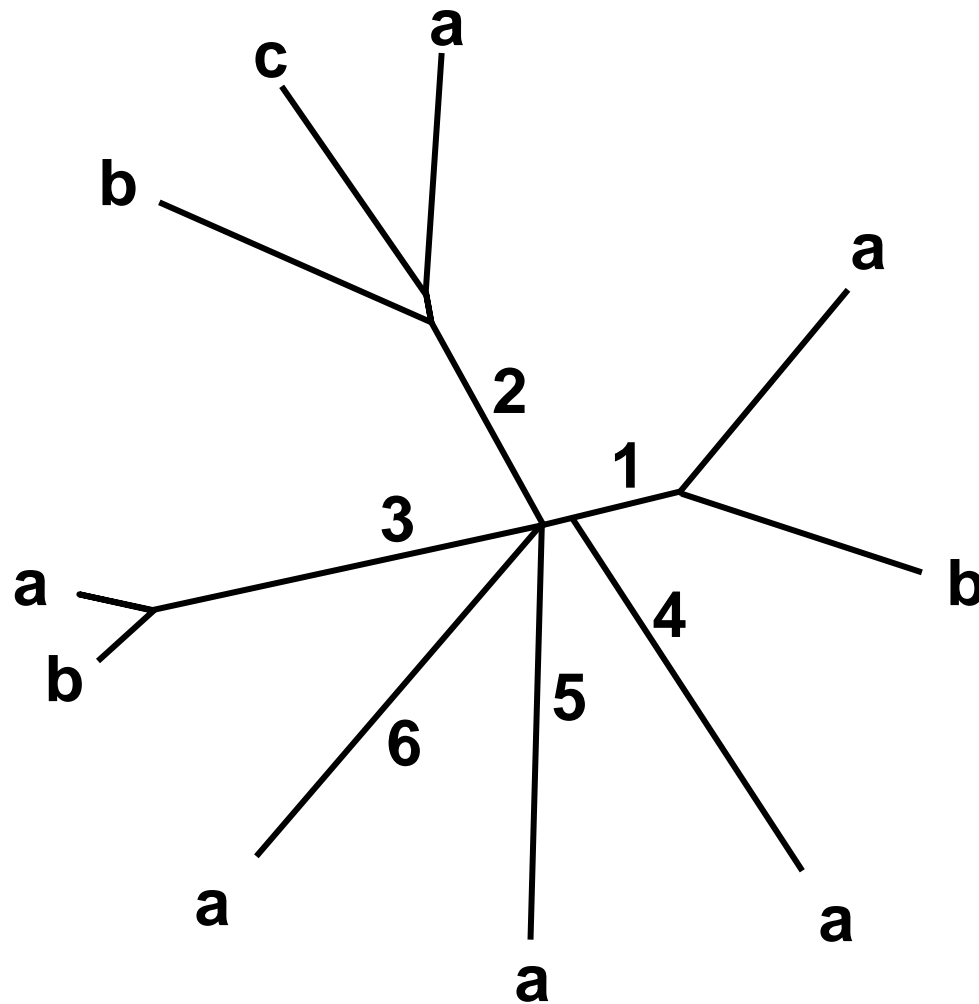
Dr. Shoshana Levy
 Dr. Sergio Abrignani
 Dr. François-Loïc Cosset



HCV Replication is Error-prone

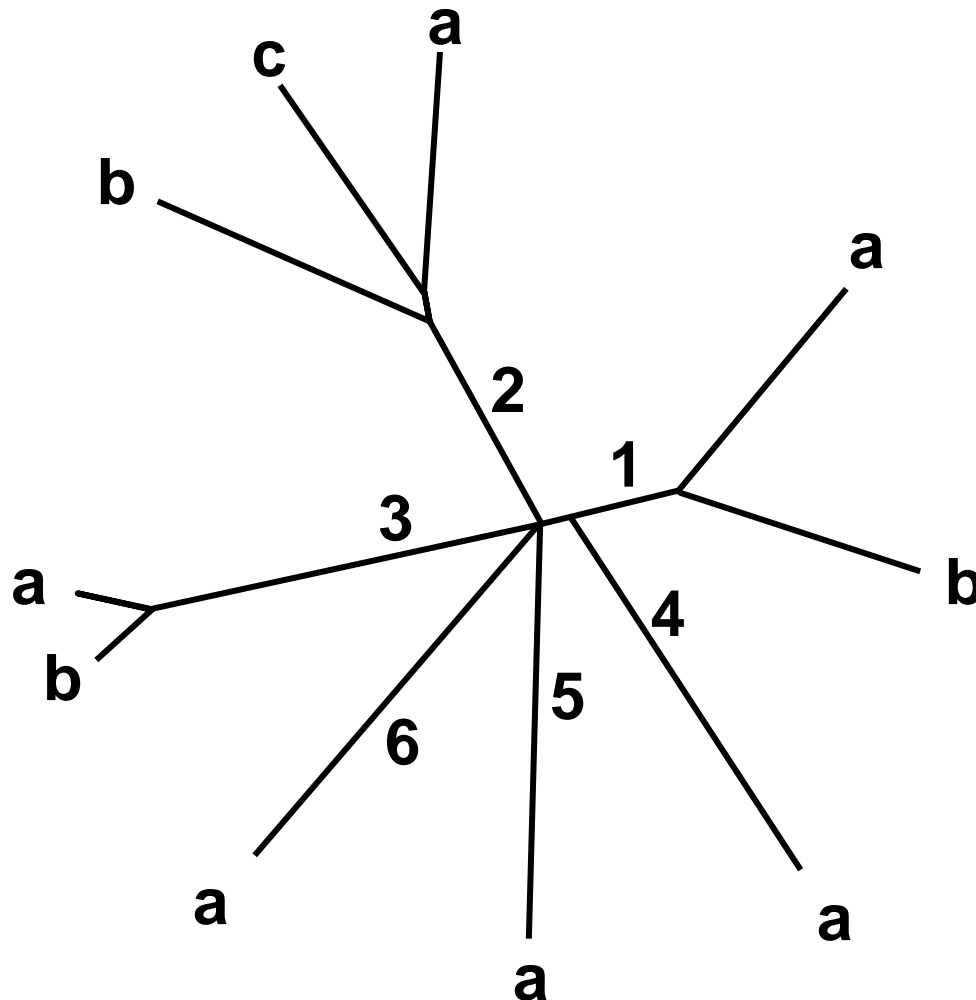


HCV Genotypes and Subtypes



Adapted from P. Simmonds J Gen Virol. 2004;85:3173-88

HCV Genotypes and Subtypes



Genotype

≥ 30% nucleotide difference

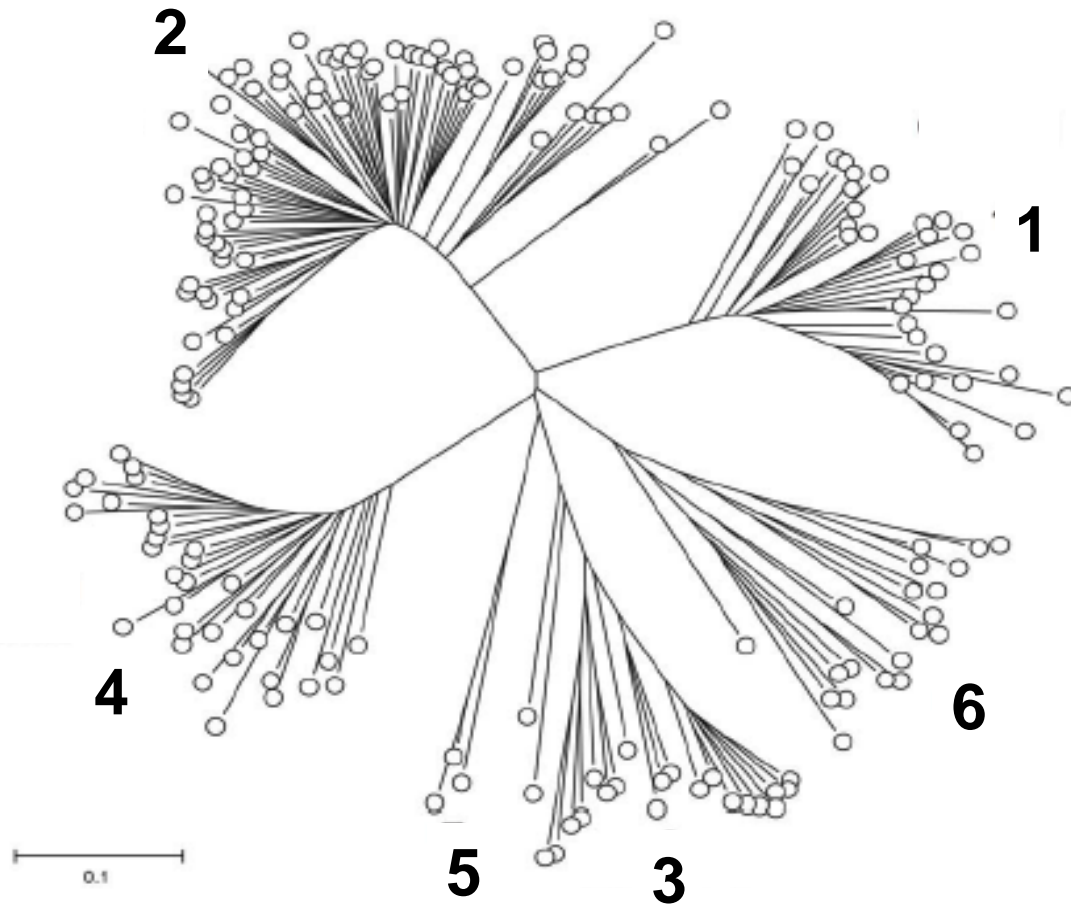
25-30% Amino acid difference

Well-established diversity

Subtype

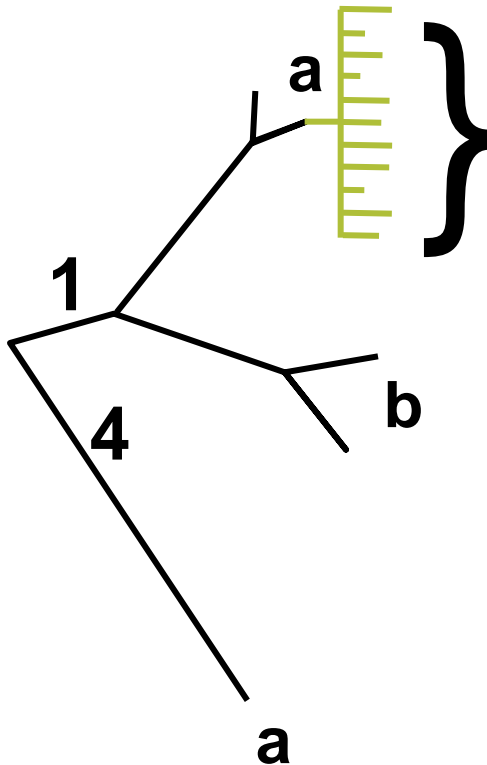
~20% nucleotide difference

Genetic Diversification of HCV: Types and Subtypes



Adapted from Simmonds J Gen Virol. 2004;85:3173-88

HCV in One Infected Person



Genotype 1a HCV
sequences retrieved
from a single person:
A Quasispecies

Genotype (population)
≥ 30% nucleotide difference
25-30% Amino acid
difference
Well-established diversity

Subtype (population)
~20% nucleotide difference

Quasispecies
(individual)
1-5% nucleotide difference

An Incredible Virus

~ 2.0×10^8 chronically infected persons worldwide

~ 1.0×10^{11} virus particles produced per day per person

~ 9.6×10^3 nucleotides per genome copy

~1 base mis-match per 5×10^3 bases copied

~ 4.0×10^{19} mutated HCV genomes generated daily worldwide

28,800 possible single-base substitutions from consensus

> 10^6 copies of each produced each day in each infected person

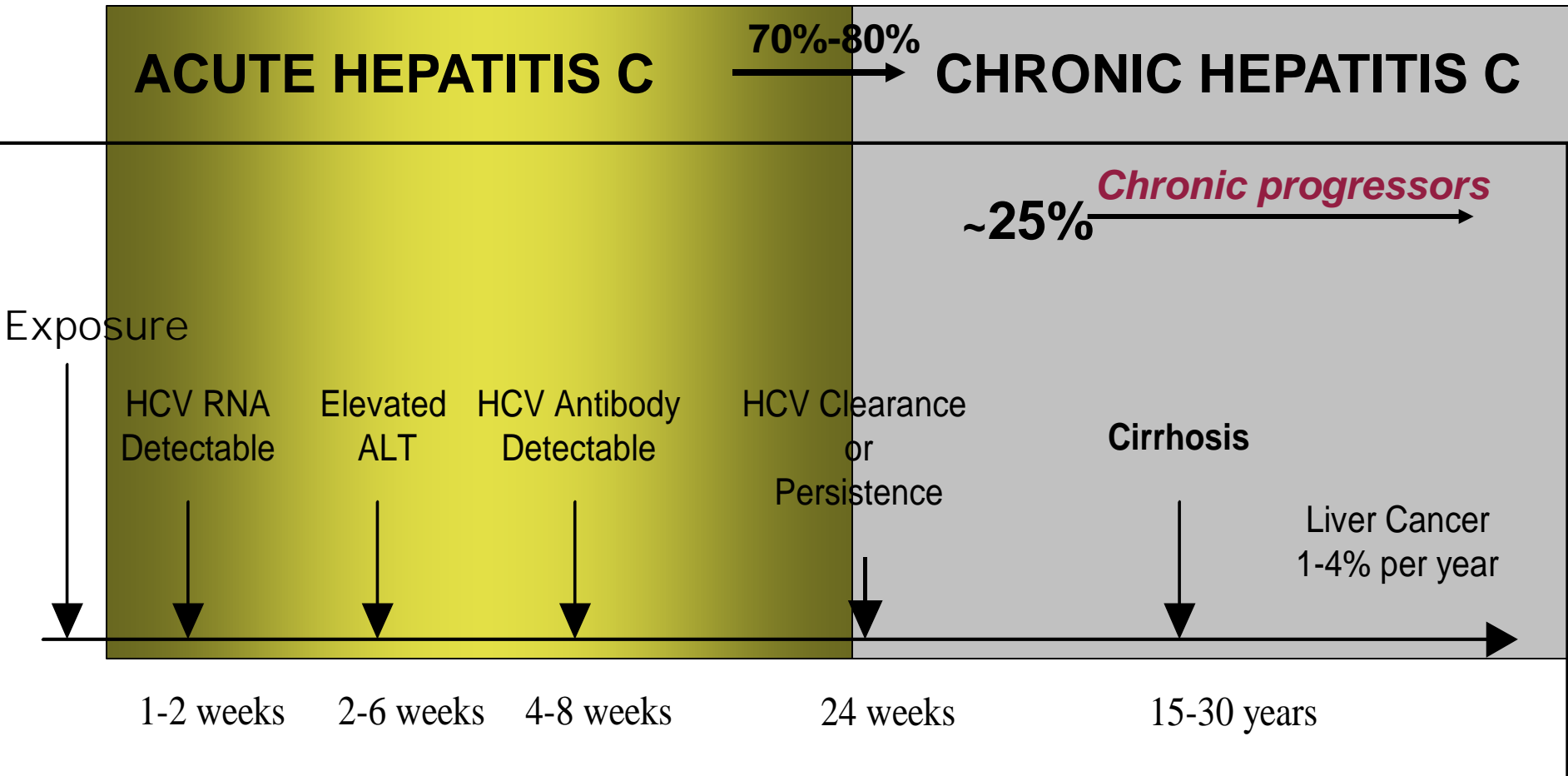
More generations of hepatitis C virus produced in one person in one day than generations of humans in the history of the world.

600 generations of virus, 300 generations of people.

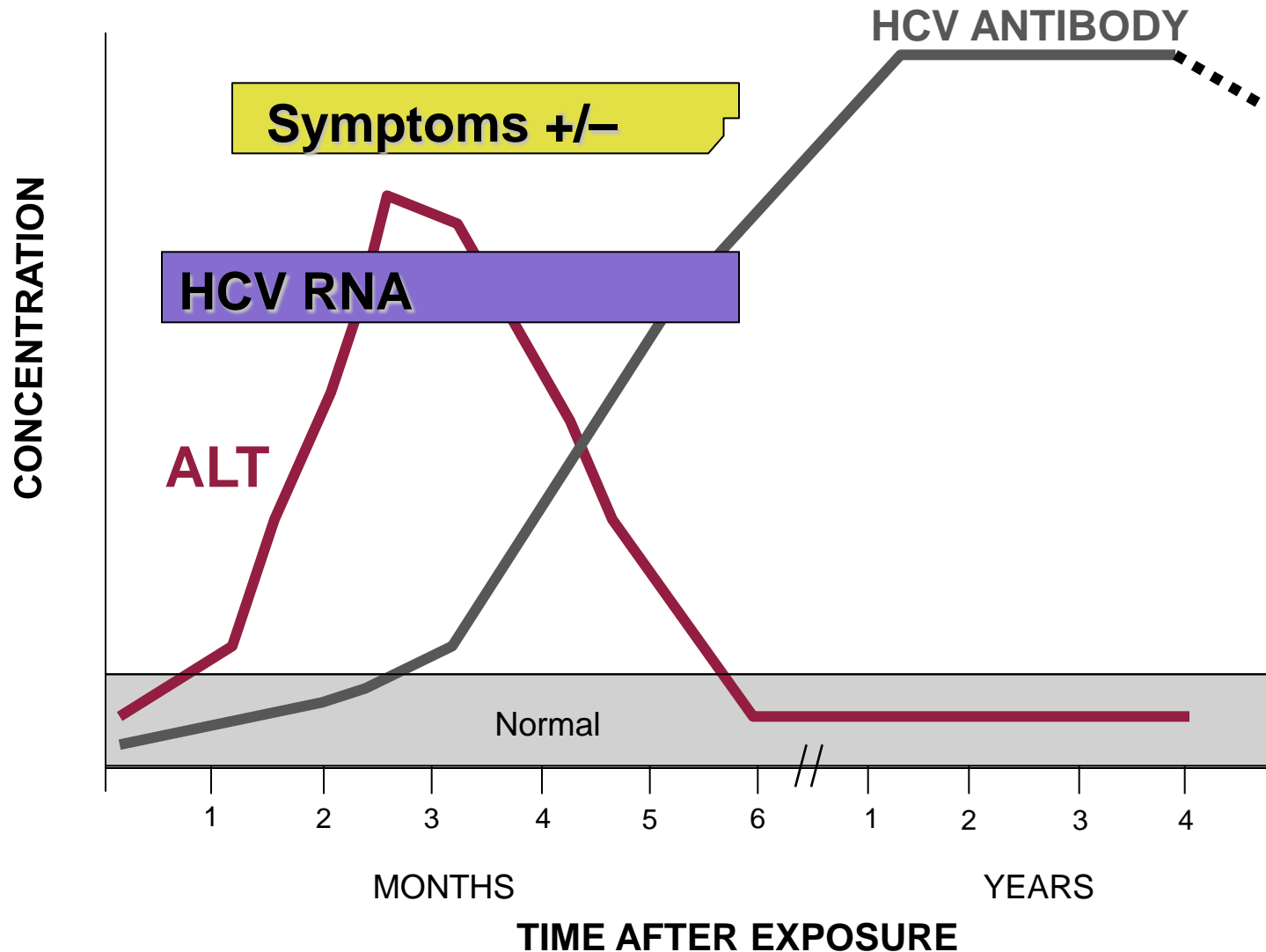
Relative Infectivity

Transmission Route	HCV Risk	HBV Risk	HIV Risk
IDU	~ 30%/yr ≥60% acute/yr	~ 12-30% acute/yr	~30%/yr
Blood Tx	Now rare	Rare	Rare
Sporadic	10% cases	20-30%	
Needle-stick	0.44-10%	3-40%	0.3%
Tattoos/Piercing	1-5%	?	? 0%
Sexual	≤5%	Highest	Higher
Vertical	≤6%	~40%	~26%
Snorting	?	~2.5% NA cases	?

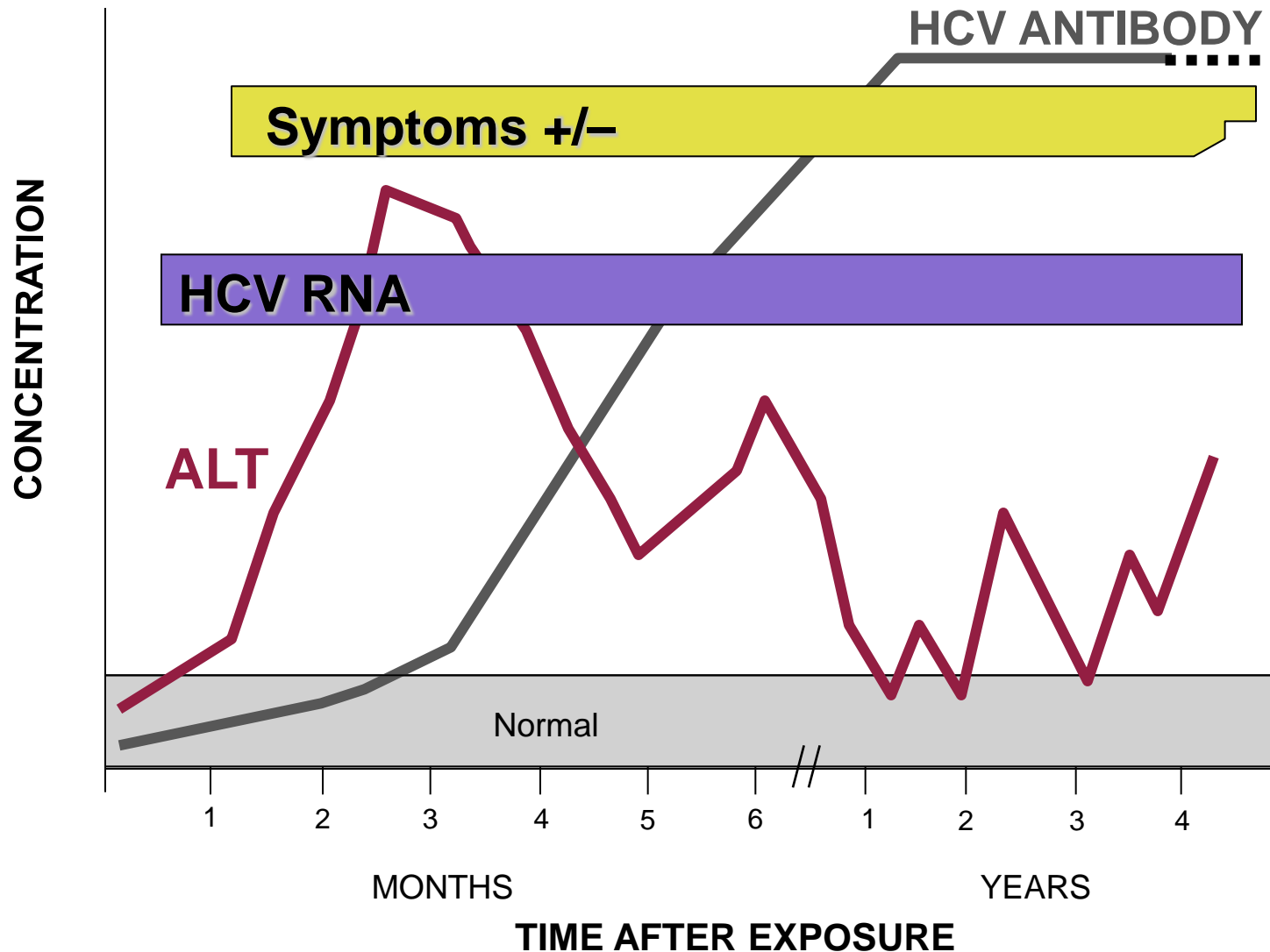
Natural History of HCV Infection



Pattern of Acute HCV Infection with Clearance



Pattern of Acute Hepatitis C with Progression to Chronic Infection



Chronic Hepatitis C

Whose Liver Disease is Progressing?

Inflammation → *Fibrosis* → *Cirrhosis*

Cells and Chemicals

Protein Fibers

Distorted Liver Architecture

→ CONTRACT ←

“FIBERS NODULES”

Staging HCV Liver Disease

- Clinical history:
 - Symptoms suggesting advanced liver disease
- Clinical Examination:
 - Evidence of Cirrhosis/Liver failure/Portal Venous \uparrow BP
- Blood Tests:
 - Evidence for disturbed liver function/blood flow
- Radiological Tests:
 - Irregular liver surface; Evidence of increased pressure in veins that drain into the liver.

Staging HCV Disease: LIVER BIOPSY

In most patients with chronic hepatitis C...

“the value of pre-treatment liver biopsy outweighs its risks”

NIH Consensus Development Statement Hepatology 2003;36(Suppl 1):S3-S20

- Grades: the amount of Inflammation
 - (METAVIR) Scale 0-4 :
 - Grade 0 = No Inflammation
 - Grade 4 = Severe Inflammation

- Stages: the amount of Fibrosis (scar tissue)
 - (METAVIR) Scale 0-4 :
 - Stage 0 = No Scarring
 - Stage 4 = Cirrhosis (Extensive fibrosis with nodular regeneration)

Why Does Staging Help?

- Interferon-based treatment is lengthy and does not cure everyone and may have significant side effects. Not everyone needs treatment.
- The degree of fibrosis has prognostic value which can influence the timing of antiviral therapy:
 - People with stage 0 fibrosis may never progress. Most can probably wait safely, at least for better therapies.
 - People with fibrosis \geq stage 2 can expect their disease to progress and should seriously consider whether to embark on therapy in the near term.
 - People with occult cirrhosis should be treated and screened for liver cancer.
- Long-term management: if cirrhosis is present liver cancer surveillance should be implemented.

People Who May Not Need Liver Biopsy

- Established Cirrhosis
- Infection with Genotypes 3 and especially 2
- Patients in whom Interferon-based treatment is contra-indicated
- *Caveat : HCC surveillance in people with cirrhosis.*

Risk Factors for Accelerated Fibrosis Progression in Chronic Hepatitis C

- Gender: Men > Women
- Race: Caucasian > African American
- Age: > 40 years old
- Duration of Infection
- Established Fibrosis on Initial Liver Biopsy
- Alcohol (intake >50g/d)
- Steatosis (Fat droplets inside liver cells)
- HBV Coinfection
- HIV Coinfection (esp. CD4 <200 // No PI) not on protease inhibitor.

VIRAL LOAD... NOT A PREDICTOR OF PROGRESSION

“Watchful Waiting” in Mild Liver Disease

- In people with \leq Stage 1 Fibrosis and low risk of accelerated disease progression
 - Repeat Liver Biopsy in 4-5 years.
- In people at high risk for accelerated progression:
 - Try to reduce risk factors
 - Repeat Liver Biopsy in 3 years.
- **Serial Biopsy Rationale: To seek evidence for disease progression**
 - Wait long enough such that progression has time to occur
 - Repeat in time to treat before advanced fibrosis develops

Advanced HCV Liver Disease

- Presence of cirrhosis implies that, unless contraindicated, antiviral therapy should be implemented in an attempt to eradicate HCV:
 - **Slow the rate of Liver disease progression**
 - **Viral clearance associated with better prognosis after liver transplantation**
- Three functional grades of cirrhosis classified by the “Child Pugh Turcotte” scoring system:
 - **A** : Liver function is preserved: Interferon usually tolerated quite well though an enhanced risk of liver failure.
 - **B** : Liver function is impaired: Greater risk for Interferon-related liver failure.
 - **C** : Liver function is severely impaired: Much greater risk for treatment-associated liver failure.

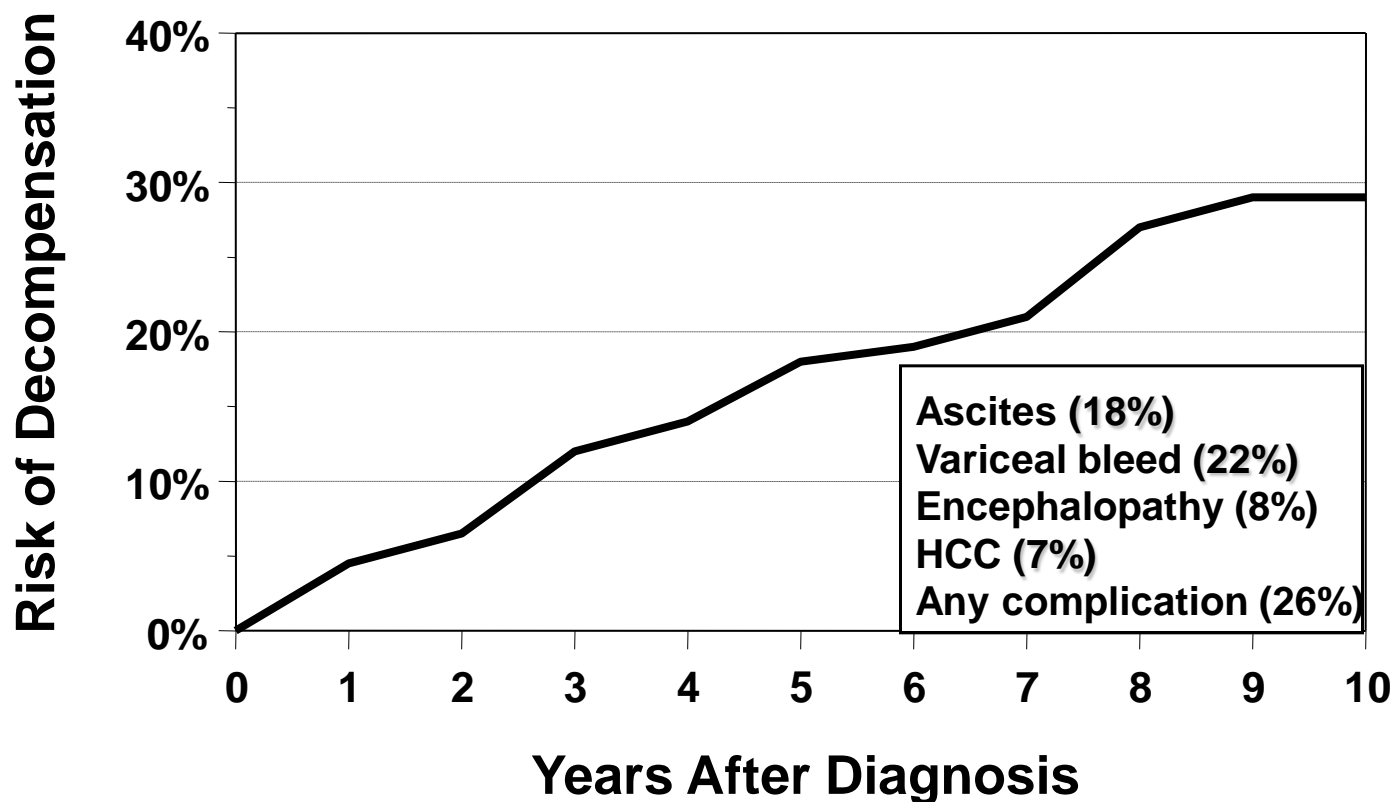
Liver Failure

(Decompensated Liver Disease)

- Liver Cell Failure leads to:
 - **Jaundice** (Bilirubin \uparrow), Bleeding (PT//INR \uparrow)
 - **Ascites**: Accumulation of fluid in the abdominal cavity secondary to portal hypertension and insufficient protein in blood (Albumin \downarrow).
 - **Variceal Bleeding**: Bursting of abnormally engorged veins, typically in the lower esophagus, into the intestine.
 - **Hepatic Encephalopathy**: Altered mental function due to build up of chemicals that the failing liver cannot remove.

Natural History of HCV Cirrhosis

Risk of Decompensation



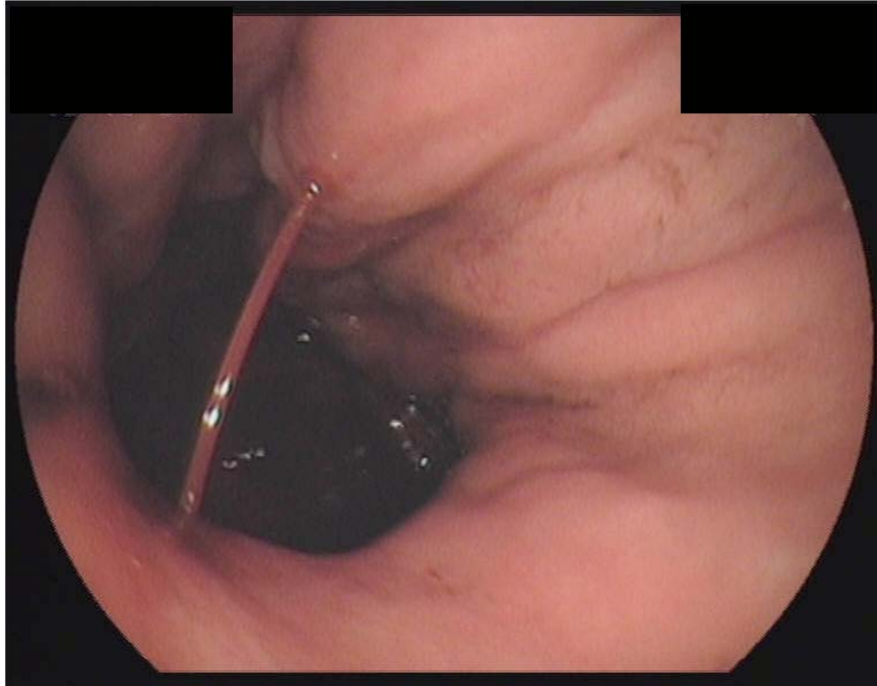
Ascites



- ~50% 2-year mortality
- Prone to bacterial infection

- **Management**
 - Salt Restriction
 - Diuretics
 - Spironolactone
 - Furosemide
 - Tap(s) (“Paracentesis”)
 - Perhaps Antibiotics
 - Liver Transplant Evaluation
 - TIPSS

Variceal Hemorrhage



- Varices in 90% portal \uparrow BP
- ~30% bleed (Bloody vomit/tarry stool)
- Overall mortality ~50%
- Bleeding/Rebleeding/Mortality ~ degree of liver impairment

- **Primary Prevention**
 - Propranolol or Nadolol
 - Band Ligation
- **Secondary Prevention**
 - Propranolol or Nadolol
 - Band Ligation
 - Sclerotherapy
 - TIPSS
 - Surgery
 - Liver Transplantation

Hepatic Encephalopathy

- **Grade 0** - Apparently normal mental status but minor changes in memory, concentration, intellect and coordination.
- **Grade 1** - Mild confusion, mood change, attention impairment. Slowed mental agility; altered sleep pattern.
- **Grade 2** - Drowsy, lethargic, gross deficits in ability to perform mental tasks, obvious personality changes, inappropriate behavior, and intermittent disorientation, usually regarding time.
- **Grade 3** - Sleepy but arousable, unable to perform mental tasks, disorientated, confused, sporadic fits of rage, incomprehensible.
- **Grade 4** - Coma with or without response to painful stimuli.

Hepatic Encephalopathy

■ Testing:

- Clinical*
- Number Connection
- Blood Chemistry: Ammonia*
- Electrophysiological
 - EEG: high-amplitude low-frequency waves and triphasic waves
 - Evoked Potentials
- MRI

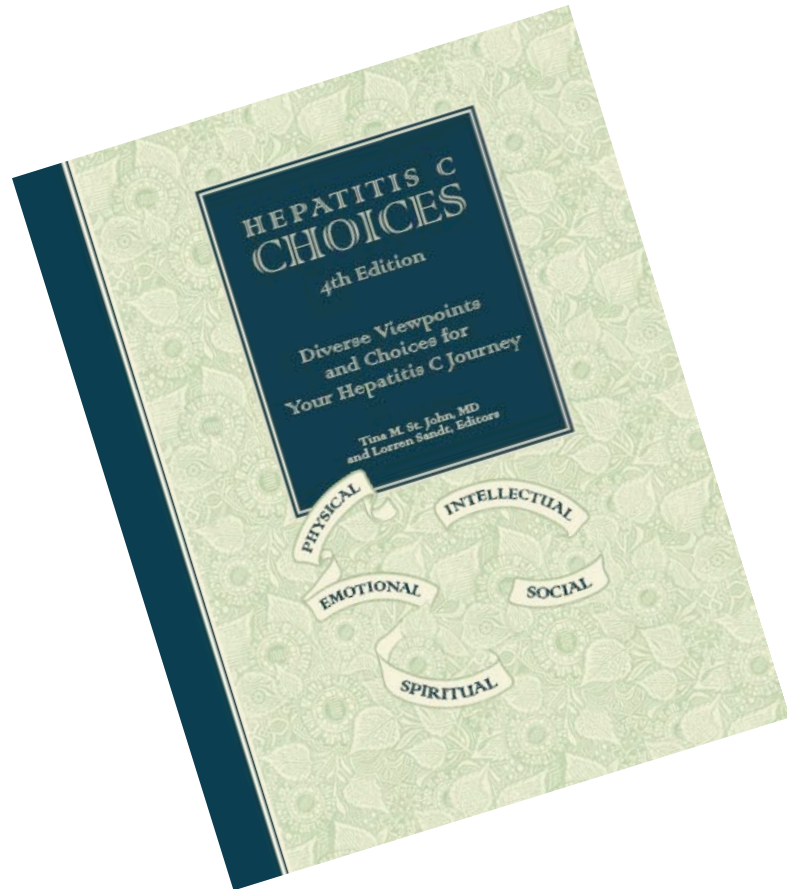
■ Treatment

- Lactulose *
- Antibiotics
 - Rifaximin
 - Neomycin
 - Metronidazole
- L-Ornithine
- Benzoate
- L-Aspartate
- Zinc
- Diet

Summary

- Test if *any* history of past exposure risk
- Infection is *not* a death sentence
- Many people do not progress or do so very slowly
- Surveillance for progressive liver disease
- Treatments are available:
 - Western therapy aims primarily at the virus and is the only therapy which cures hepatitis C
- More treatments showing promise in clinical trials and are on the horizon

For more information



Chapter 2: Overview of Hepatitis C

http://www.hepcchallenge.org/choices/pdf/Chapter_02_OL.pdf

Visit us on line at www.HepCChallenge.org